Risk of suicide in users of β-adrenoceptor blockers, calcium channel blockers and angiotensin converting enzyme inhibitors

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Aims To examine the risk of suicide in users of β-adrenoceptor blockers, calcium channel blockers, and angiotensin converting enzyme inhibitors.

Methods We conducted a cohort study based on linkage of a population-based prescription registry in North Jutland County, Denmark, and the nationwide Death Registry. From 1989 to 1995 there were 58 529 users of β-adrenoceptor blockers, calcium channel blockers, and angiotensin converting enzyme inhibitors. The mortality rates from suicides in the cohort members were compared with the rates in the general population.

Results One hundred and four suicides occurred in the cohorts. The standardized mortality ratio for suicide in users of β-adrenoceptor blockers was 1.6 (95% confidence interval: 1.2–2.1), in users of calcium channel blockers 1.2 (95% confidence interval: 0.8–1.7), and in users of angiotensin converting enzyme inhibitors 1.2 (95% confidence interval: 0.7–1.8). In users of β-adrenoceptor blockers, the risk of suicide was increased during the first 12 months after the start of therapy, standardized mortality ratio 2.1 (95% confidence interval: 1.2–3.5). There was a trend in the standardized mortality ratio of suicide from 0.9 (95% confidence interval: 0.4–1.9) in users of β-adrenoceptor blockers with low lipid solubility, to 1.6 (0.8–2.8) and 2.7 (1.7–4.1) in users of β-adrenoceptor blockers with medium and high lipid solubility, respectively.

Conclusions Users of medium and high lipid soluble β-adrenoceptor blockers may have an increased risk of suicide. Users of calcium channel blockers and angiotensin converting enzyme inhibitors do not seem to have a significantly increased risk of suicide.

Keywords: angiotensin enzyme inhibitors, β-adrenoceptor blockers, calcium channel blockers, depression, epidemiology, suicide

Introduction

It was suggested more than 30 years ago [1] that β-adrenoceptor blockers may induce depression, though the existing studies have given conflicting results [2–8]. Case reports [9–11] have also suggested a link between calcium channel blockers and depression, and in a recent paper from Sweden, Lindberg *et al.* expressed concern that calcium channel blockers may increase the risk of suicide [12]. Based on five suicides in 617 calcium channel blocker users, they found a statistically significant increased risk of 5.4 of suicide compared with four suicides in 2780 nonusers [12]. The finding was supported in the same paper by data from a cross-sectional ecological study that included 152 of Sweden's 284 municipalities [12], but could not be confirmed in a recent British case-control study [13]. Few data exist on angiotensin converting enzyme (ACE) inhibitors, but recent case-control [14] and prescription analyses indicated that ACE-inhibitors may have a depression-inducing effect.

β-adrenoceptor blockers, calcium channel blockers, and ACE-inhibitors are widely used, and even a small excess risk of suicide has major public health implications.

In this population-based study from the county of North Jutland, Denmark, the mortality rates from suicide were assessed in large cohorts of users of β-adrenoceptor

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blockers, calcium channel blockers, and ACE-inhibitors, and compared with the rate of suicide in the general population of the country.

Methods

Study population

The Pharmaco-Epidemiological Prescription Database of North Jutland County [15], initiated on 1 January 1989, was used to identify individuals with ever use of drugs until 31 December 1995: β-adrenoceptor blockers, 31 462; calcium channel blockers, 27 788; ACE-inhibitors, 17 897 (Table 1). Due to overlap between the three groups, the study covered 58 529 different individuals residing in the county (population 490 000), on the basis of 923 758 prescriptions.

The county is served by 33 pharmacies with computerized accounting systems, from which data are sent to the Danish National Health Service, which provides tax-supported health care for all inhabitants of the county and refunds 50–75% of the costs of prescribed pharmaceuticals. The data that are transferred to the Prescription Database include the customer's personal identification number (which incorporates sex and date of birth), the type of drug prescribed according to the anatomical therapeutical chemical (ATC) classification system [16] and the date of prescription.

Drug exposures

The prescriptions included: (i) β-adrenoceptor blockers, including propranolol (27.5% of all β-adrenoceptor blocker prescriptions), atenolol (25.8%), metoprolol (20.3%), betaxolol (2.7%), alprenolol (2.0%), and others (6.4%); (ii) calcium channel blockers – diltiazem (32.6%), verapamil (31.2%), amlodipine (12.9%), felodipine (9.7%), nifedipine (7.3%), and others (6.3%); and (iii) ACE-inhibitors – captopril (32.5%), enalapril (26.4%), lisinopril (14.4%), perindopril (7.4%), and others (18.7%).

β-adrenoceptors blockers were further subgrouped into three categories according to their lipid solubility, i.e. low, medium, and high [17]. β-adrenoceptor blockers with high lipid solubility pass the blood–brain barrier, and it has

Table 1 Descriptive characteristics and person-years of follow-up in users of cardiovascular drugs; prescription data between 1 January 1989 and 31 December 1995.

	β-adrenoceptor blockers		*Calcium channel blockers*		*ACE- inhibitors*	
Variable	*Number*	*%*	*Number*	*%*	*Number*	*%*
Ever users*	31 462	(100)	27 788	(100)	17 897	(100)
Men	13 029	(41)	13 636	(49)	8 865	(50)
Women	18 433	(59)	14 152	(51)	9 032	(50)
Year of first entry[1]						
1989	9106	(29)	5515	(20)	2248	(13)
1990	4120	(13)	3077	(11)	1896	(11)
1991	3418	(11)	3859	(14)	2394	(13)
1992	3627	(12)	4040	(15)	2763	(15)
1993	3565	(11)	3800	(14)	2674	(15)
1994	3990	(13)	4035	(14)	3027	(17)
1995	3636	(11)	3462	(12)	2895	(16)
Age at first entry (years)						
<49	10 677	(34)	4271	(16)	3842	(21)
50–64	9632	(31)	8667	(31)	5838	(33)
65–79	9278	(29)	11 719	(42)	6507	(36)
≥ 80	1875	(6)	3313	(11)	1710	(10)
Person-years of follow-up						
Total	118 558		89 295		52 151	
Average (range)	3.8 (0–7)		3.2 (0–7)		2.9(0–7)	
Ever use of other drugs[2]						
Antidepressants	5287	(17)	4597	(17)	2834	(16)
Neuroleptics	4785	(15)	4251	(15)	2342	(13)
Statins	422	(1)	496	(2)	258	(2)
Migraine drugs	2232	(7)	934	(3)	574	(3)

*The study covers a total of 58 529 different individuals of whom a considerable number is included in two or three user groups.

[1]Date of first prescription of the relevant drug.

[2]Ever use of the drugs in the cohort during the period 1 January 1989 to 31 December 1995.

been claimed that such compounds are associated with a higher incidence of central nervous system side-effects than the others [17]. In Denmark the registered indications [18] during the study period for β-adrenoceptor blockers were: angina pectoris, hypertension, secondary prophylaxis after acute myocardial infarction, arrhythmia, thyrotoxicosis, familial and senile tremor, migraine, and portal hypertension; for calcium channel blockers: angina pectoris, hypertension, prophylaxis after acute myocardial infarction, and arrhythmia; and for ACE-inhibitors: hypertension and heart failure.

In order to investigate the prevalence among participants of medical conditions and treatments possibly predisposing to suicide, such as depression, psychotic conditions, migraine, or treatment with statins, we also obtained information from the Prescription Database on use of antidepressants, neuroloptics, migraine drugs and statins during the entire period 1989–95.

Causes of death

Participants were linked to the National Death Certificate files, which include information on date and cause of death of all inhabitants of Denmark, classified according to the *International Classification of Diseases*, 8th Revision (ICD-8) during 1989–93, and then the 10th Revision (ICD-10) [19]. Our main outcome variable was death due to suicide, which is verified in all cases by a public health officer or at a department of forensic medicine. However, in order to assess mortality from diseases that possibly predispose to suicide, we also sought information on other causes of death among cohort members including diabetes, liver diseases, bronchitis, emphysema, asthma, and cardiovascular diseases.

Statistical analyses

The main analysis compared the observed numbers of deaths in each cohort of ever users of β-adrenoceptor blockers, calcium channel blockers, or ACE-inhibitors with those expected from the mortality in the general population. Follow-up was from the date of the first known prescription of the respective drug to the date of death, or 31 December 1995, whichever occurred first. The expected number of deaths was calculated by multiplying the number of person-years of cohort members by the county-specific mortality rates for each sex, in 5 year age groups and calendar periods of observation. Standardized mortality ratios (SMR) served as a measure of the relative mortality, and 95% confidence intervals were calculated, assuming a Poisson distribution of the observed deaths [20].

A further analysis was restricted to individuals who were exclusive users of β-adrenoceptor blockers ($n=26\,758$), calcium-channel blockers ($n=20\,142$), or ACE-inhibitors ($n=11\,718$). A given prescription was assumed to cover a maximum of 180 days (present use), after which the participant was regarded as a former user, unless a new prescription was issued. A former user could reenter the present use period if a new prescription was registered, but hereafter the person was not allowed to reenter the former use period. Follow-up of present and former users was ended at the date of the start of treatment with one of the two other drugs, death, or 31 December 1995. The group of present and former users of β-adrenoceptor blockers was stratified according to the degree of lipid solubility of the compound.

Results

The sex distribution of ever users of calcium channel blockers and ACE-inhibitors was almost equal, but more women than men were treated with β-adrenoceptor blockers (Table 1). No differences in the use of antidepressants, neuroleptics, and statin drugs were found. There were twice as many users of migraine drugs among users of β-adrenoceptor blockers than among members of the other two cohorts.

Table 2 shows the overall mortality and the mortality from selected causes for ever use in each cohort. The suicide risk was significantly increased in users of β-adrenoceptor blockers: 53 observed suicides *vs* 32.4 expected (SMR: 1.6), and slightly but not significantly increased in calcium channel blocker users (SMR: 1.2) and ACE-inhibitors (SMR: 1.2). Cardiovascular mortality was increased by 1.6 fold in β-adrenoceptor blocker users, two-fold in calcium channel blocker users, and three-fold in ACE-inhibitors users. The mortality due to bronchitis and diabetes was increased among users of calcium channel blockers and ACE-inhibitors. A slightly increased mortality due to liver cirrhosis was found among users of β-adrenoceptor blockers, but none of the 40 suicides in present and former users of β-adrenoceptor blockers had been admitted to a hospital in the county for liver cirrhosis before the suicide.

Table 3 shows the SMRs from suicide in exclusive users of β-adrenoceptor blockers ($n=26\,758$), calcium channel blockers ($n=20\,142$), and ACE-inhibitors ($n=11\,718$). The increased risk of suicide seen among present users of β-adrenoceptor blockers was apparently limited to the first year of use (SMR: 2.1, 95% confidence interval: 1.2, 3.5). Similarly, the SMR for suicide among former users of β-adrenoceptor blockers was increased (SMR: 2.9, 95% confidence interval: 1.7, 4.7), particularly among the subset of persons who had received at least three prescriptions during the period of use (SMR: 4.3, 95% confidence interval: 1.6, 9.4, $n=6$, data not shown in table).

Table 2 Number of deaths from suicide, accidents, and cardiovascular disorders, and associated standardized mortality ratios (SMRs) among individuals who ever used beta-blockers, calcium channel blockers or angiotensin converting enzyme inhibitors, 1989–1995.

	β-adrenoceptor blockers		*Calcium channel blockers*		*ACE-inhibitors*	
Variable	*Obs*	*SMR (95% CI)*	*Obs*	*SMR (95% CI)*	*Obs*	*SMR (95% CI)*
Cause of death						
All causes	3662	1.24 (1.20, 1.29)	4985	1.50 (1.46, 1.54)	2871	2.02 (1.95, 2.09)
Suicide	53	1.6 (1.2, 2.1)	33	1.2 (0.8, 1.7)	18	1.2 (0.7, 1.8)
Accidents	116	1.0 (0.9, 1.3)	117	0.9 (0.8, 1.1)	64	1.2 (1.0, 1.6)
Cardiovascular disorders	2013	1.56 (1.49, 1.63)	3078	2.02 (1.95, 2.09)	1851	2.99 (2.86, 3.13)
Hypertension	69	4.1 (3.2, 5.2)	69	3.7 (2.9, 4.7)	49	6.0 (4.4, 7.9)
Ischaemic heart disease	1280	1.7 (1.6, 1.8)	2158	2.5 (2.4, 2.6)	1262	3.5 (3.3, 3.7)
Cerebrovascular diseases	368	1.3 (1.2, 1.4)	434	1.3 (1.2, 1.4)	215	1.6 (1.4, 1.8)
Other cardiovascular disorders	296	1.2 (1.1, 1.4)	417	1.4 (1.3, 1.6)	325	2.8 (2.5, 3.1)
Other causes						
Liver cirrhosis, cholelithiasis and cholecystitis	56	1.8 (1.4, 2.3)	22	0.8 (0.5, 1.1)	20	1.3 (0.8, 2.0)
Bronchitis, emphysema and asthma	59	0.5 (0.4, 0.6)	189	1.3 (1.1, 1.5)	111	1.7 (1.4, 2.0)
Diabetes	60	1.4 (1.0, 1.8)	105	2.2 (1.8, 2.7)	104	5.0 (4.1, 6.1)

Table 3 Number of deaths from suicide and associated standardized mortality ratios (SMRs) in users of beta-blockers only ($n=26\,758$), users of calcium channel blockers only ($n=20\,142$) and users of angiotensin converting enzyme inhibitors only ($n=11\,718$).

	β-adrenoceptor blockers		*Calcium channel blockers*		*ACE-inhibitors*	
User status/characteristics	*Number observed*	*SMR (95% CI)*	*Number observed*	*SMR (95% CI)*	*Number observed*	*SMR (95% CI)*
Present users						
Men	17	1.7 (1.0, 2.7)	12	1.3 (0.6, 2.2)	7	1.4 (0.6, 3.1)
Women	7	1.0 (0.4, 2.0)	4	1.0 (0.3, 2.6)	1	
Both sexes	24	1.4 (0.9, 2.1)	16	1.2 (0.7, 1.9)	8	1.2 (0.5, 2.4)
Years of follow-up						
< 1	15	2.1 (1.2, 3.5)	7	1.2 (0.5, 2.3)	2	0.6 (0.1, 2.3)
1–4	9	1.0 (0.4, 1.8)	8	1.1 (0.1, 3.3)	6	1.7 (0.6, 3.7)
5+	0		1		0	
Former users*						
Men	7	2.2 (0.9, 4.6)	4	1.5 (0.4, 3.8)	1	1.1 (0.0, 6.1)
Women	9	3.9 (1.8, 7.4)	2	1.8 (0.2, 6.3)	1	2.2 (0.0, 12.3)
Both sexes	16	2.9 (1.7, 4.7)	6	1.6 (0.4, 3.4)	2	1.5 (0.2, 5.3)

*No treatment with any of the two other medications.

Table 4 shows the number of deaths from suicide and the associated SMRs by degree of lipid solubility of the β-adrenoceptor blocker being used. There was a significantly increased trend in the SMR of suicide from 0.9 (95% confidence interval: 0.4–1.9) in users of β-adrenoceptor blockers with low lipid solubility to 1.6 (0.8–2.8) and 2.7 (1.7–4.1) in users of β-adrenoceptor blockers with medium and high lipid solubility, respectively (Table 4). In a separate analysis we excluded 1182 persons who had a prescription for migraine drugs before or concurrent with the β-adrenoceptor blocker prescription. The SMRs for the low lipid solubility group were (present and former, present, former use) 0.9; 0.7; 2.0. For the medium group 1.4; 1.2; 2.4, and for the high lipid group: 2.3; 2.0; 3.0. In general, the SMRs were reduced only slightly in the restricted group of users.

Discussion

We found an association between medium and high lipophilic β-adrenocpetor blockers and suicide, but no association with use of β-adrenocpetor blockers with low lipid solubility. The risk was increased during the first year of treatment, and in the years following discontinuation of treatment. The dose–response association between the degree of lipid solubility and risk of suicide may suggest a causal association although a higher prevalence of individuals with migraine in the cohort of β-adrenoceptor

Table 4 Number of deaths from suicide and associated standardized mortality ratios (SMRs) in current and former users of β-adrenoceptor blockers only, by degree of lipid solubility of the drug.

	β-adrenoceptor blockers only						
	Present and former use			*Present use*		*Former use*	
Degree of lipid solubility	*Number observed*	*Number expected*	*SMR (95% CI)*	*Number observed*	*SMR (95% CI)*	*Number observed*	*SMR (95% CI)*
Low*	7	7.8	0.9 (0.4, 1.9)	4	0.6 (0.2, 1.6)	3	2.0 (0.4, 5.7)
Medium[1]	11	7.1	1.6 (0.8, 2.8)	8	1.4 (0.6, 2.7)	3	2.3 (0.5, 67)
High[2]	22	8.0	2.7 (1.7, 4.1)	12	2.2 (1.1, 3.9)	10	3.8 (1.8, 7.0)
Chi square test for trend, *P* value:		0.04			0.06		0.62

*Low group: atenolol; sotalol.

[1]Medium group: metoprolol; pindolol; acebutolol; oxprenolol; timolol; Viskaldix; bisprolol; bevantolol.

[2]High group: propranolol; betaxolol; alprenolol; penbutolol.

Person-years at risk among present users were categorized according to the type of β-adrenoceptor blocker prescribed, and those among former users in accordance with the type of the last β-adrenoceptor blocker prescribed.

blocker users may explain part of the excess. The lipid soluble β-adrenoceptor blockers pass the blood brain barrier, and it has been suggested that biogenic amine depletion may play a role in the relation between antihypertensive medication and depression [21, 22]. The hydrophilic β-adrenoceptor blockers should in theory have fewer effects on the central nervous system, but the existing data are sparse and inconsistent [8, 21].

The risk of suicide in persons taking β-adrenoceptor blockers could be influenced by confounding by indication, confounding by comedication and other types of bias that may operate in different directions. The following confounding factors may tend to overestimate the risk estimates. Serious conditions like cardiovascular disease, pulmonary obstructive disease, and diabetes may affect the risk of suicide [23]. However, we do not think that this has influenced the results for β-adrenoceptor blockers substantially, because the mortality from these diseases was higher for users of calcium channel blockers and ACE-inhibitors without any major effect on the risk of suicide.

However, the following diseases may affect the risk estimates in the other direction. β-adrenoceptor blockers are also used in the treatment of liver cirrhosis with portal hypertension and migraine, of which at least migraine may be a risk factor for suicide [24]. Users of β-adrenoceptor blockers had a higher mortality from liver disease than users of the two other drugs, but none among the persons that committed suicide. Migraine has, as mentioned, been suggested as a risk factor for suicide, but after restriction of the β-adrenoceptor blocker users to those being nonusers of migraine drugs, we still observed a dose–response effect of lipid solubility on the risk of suicide, although the effect was slightly smaller than without the restriction. Though β-adrenoceptor blockers are not used specifically to treat depression and other psychiatric diseases, such conditions are worth considering because of the close link between these conditions and suicide. From data on the use of antidepressants and neuroleptics, we saw no indication of differences in the prevalence of use of these types of drugs among users of the three types of antihypertensive drug. Psychiatric diseases are associated with accidents [25], but we did not find any differences in accident mortality. Use of comparison rates from the general population may also lead to overestimation of the risk, and may explain a part of the slightly elevated risk in users of calcium channel blockers and ACE-inhibitors, but not the entire association between high lipid soluble β-adrenoceptor blockers and suicide. Concomitant use of statins, also under suspicion for increasing the risk of suicide, was very low in all three cohorts.

The higher risk of suicide among former β-adrenoceptor blocker users compared with present users is probably seen because doctors are inclined to discontinue treatment with β-adrenoceptor blockers if signs and symptoms of depression occur because depression is described as a side-effect of β-adrenoceptor blockers in the Danish Pharmacopoeia [18]. This phenomenon is likely to be present independently of the reason for the increased risk of suicide among users of β-adrenoceptor blockers, and is not necessarily a sign of confounding by indication. In addition, the pronounced risk of suicide among former users of β-adrenoceptor blockers may reflect a prolonged suicide effect of β-adrenoceptor blockers. Since we found an increased risk in former users of all three types of drugs, progression of the underlying disease, for instance, heart failure, would probably also lead to cessation of the treatment in some cases.

Our study has the advantage of being able to collect information on drug use from a complete follow-up of

study subjects for suicides using the national mortality files. Selection and information bias are thus unlikely. The 10-digit personal identification number basically eliminates loss to follow-up due to mislinkage of register information [15].

The existing studies regarding the risk of depression in users of β-adrenoceptor blockers have been conflicting [2–8, 14]. Possible explanations include differences in study design, case definition and confounding disease states [16]. These studies did not use suicide as an end point, which is probably a specific but nonsensitive indicator of severe depression. Our data also clearly show that combining hydrophilic and lipophilic β-adrenoceptor blockers may attenuate the findings about an association. A slight, not significant increased risk for suicide was found for calcium channel blockers and ACE-inhibitors. By contrast with a recent report [12], showing a significant risk in calcium channel blocker users, our study found a nonsignificant 20% increased risk in calcium channel blocker users. The reasons for the different results are unclear, but may be related to the exposure measured in the two studies.

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